# PATENT SPECIFICATION

606,962

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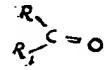
COMPLETE SPECIFICATION

## Improvements in or relating to the Preparation of Substituted Cyanoacetic Esters

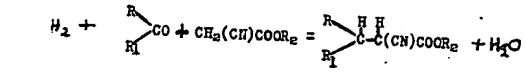
We, SHARP & DOHME, INCORPORATED, a Corporation organised and existing under the laws of the State of Maryland, United States of America, of 640, North Broad Street, Philadelphia, Pennsylvania, United States of America, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

This invention relates to an improved process for the preparation of a mono-alkyl or -aralkyl cyanoacetic alkyl ester which comprises reacting a ketone or an aldehyde of the general formula—



wherein R is hydrogen, an alkyl (including cycloalkyl) or an aryl radical and $R_1$ is an alkyl (including cycloalkyl) radical or may be an aryl radical when R is hydrogen, or R and $R_1$ may together form a cycloalkyl radical with a cyanoacetic alkyl ester in the presence of an alkali metal salt of a fatty acid, or an acid amide, or a soluble salt of a nitrogen base, in the presence of hydrogen and a hydrogenation catalyst.

The process of the invention may be illustrated by the following equation:



wherein R is hydrogen, an alkyl (including cycloalkyl) or an aryl radical and $R_1$ is an alkyl (including cycloalkyl) radical or may be an aryl radical when R is hydrogen, and $R_2$ is an alkyl radical.

The process is of particular advantage for the production of mono-alkyl cyanoacetic esters in which the mono-alkyl group is lower as well as a higher alkyl radical such as the hexyl, heptyl, octyl and the like radicals, and even higher, including both straight and branched chain alkyl radicals. In general, the mono-alkyl or -aralkyl derivatives resulting from the procedure are saturated in the aliphatic portions thereof and without any hydrogenation of any benzene radicals which they may contain.

A wide range of ketones may be condensed with cyanoacetic alkyl esters in accordance with the present invention, including open chain ketones, such as acetone, methylethyl ketone, methyl-*n*-propyl ketone, methyl-*n*-amyl ketone, di-*n*-propyl ketone, mesityl oxide, diethyl ketone, as well as cyclic ketones, such as *cyclo*-hexanone, *cyclo*pentanone and aryl-alkyl ketones, such as acetophenone, propiophenone, butyrophenone.

A similar wide range of aldehydes may be condensed with the alkyl cyanoacetic esters, including open chain aldehydes, straight or branched, such as acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, heptaldehyde, as well as cyclic aldehydes as *cyclo*pentylaldehyde, *cyclo*hexylaldehyde and including aryl aldehydes such as benzaldehyde.

The alkyl radical ($R_2$ above) in the cyanoacetic alkyl ester starting material may be any suitable alkyl group such as hereinabove indicated for the other alkyl groups and advantageously a lower alkyl group.

In general, the invention includes the reaction when carried out in the presence of a condensing agent consisting of a soluble salt of a nitrogen base (which may

be primary, secondary or tertiary), i.e. an ammonium or amine base or an alkali metal salt of a fatty acid, or an acid amide, such as acetamide. Preferably, the salts which are used are the acetates of the bases, such as diethylamine acetate, monoethylamine acetate, triethylamine acetate, ammonium acetate, piperidine acetate. Compounds or condensing agents which have been found to have important advantages for carrying out the condensation are the acetates of primary or secondary amines, or even tertiary amines particularly with the aldehydes, or ammonium acetate, which enable the condensation to be accomplished with particularly good yields of the desired product in fairly pure state and with a minimum of side reactions, such as polymerization. Ammonium acetate, on heating, is converted into acetamide. This substance, which may be formed *in situ* in certain of the reaction mixtures in which ammonium acetate is used as the catalyst, is in itself a good catalyst for these reactions, and may be introduced directly into the reaction mixture to effect the condensation; or, solutions of soluble salts of nitrogen bases in acetamide may be used with advantage.

An important specific aspect of the invention lies in the use of such a condensing agent in the presence of a fatty acid for which purpose acetic acid is particularly important. Instead of using acetamide as the condensing agent in such an acid solution, other amides and other soluble salts may be used, with improved results as compared with the use of such soluble salts and amides alone. When the reaction is carried out in the presence of an acid such as acetic acid, an additional solvent, such as benzene or other inert solvent may be used or the acid itself may be used as the solvent.

Various hydrogenation catalysts, particularly a hydrogenation catalyst having an activity about the same as that of metals of the platinum and palladium group may be used. Preferred are catalysts selected from the platinum and palladium group, viz. any of the six metals forming the two triads in Group VIII and in particular platinum and palladium. A catalyst which is particularly advantageous for the hydrogenation is palladium supported on charcoal. This catalyst may be prepared, for example, by agitating a powdered charcoal, such as pure animal charcoal, with an aqueous solution of palladium chloride in an admosphere of hydrogen. A suitable proportion is about 1 part of palladium chloride to 6 parts of charcoal. Agitation should be continued until the palladium chloride is reduced and the palladium is deposited on the charcoal. The catalyst may then be filtered off, washed and dried. It is then ready for immediate use in the process, or it may be kept *in vacuo* over sulphuric acid until used. This catalyst may be used with advantage.

While in the broad aspect, the reaction conditions are generally substantially the same with respect to the carbonyl compound (ketone or aldehyde) starting material selected, the optimum experimental conditions for the reaction vary slightly according to the type of carbonyl compound used. For example, in the examples below, piperidine acetate and acetic acid were employed with particular effectiveness with the aldehydes, and ammonium acetate and acetic acid was used with the ketones. When ethyl cyanoacetate was reacted with ketones, alcohol served as a most satisfactory solvent for use in carrying out the process of the invention. Dioxane served most satisfactorily as a solvent in reacting ethyl cyanoacetate with higher aldehydes (e.g. isobutyraldehyde, isovaleraldehyde, heptaldehyde and benzaldehyde), with glacial acetic acid serving as a most satisfactory solvent when reacting the lower molecular weight aldehydes as acetaldehyde, propionaldehyde and butyraldehyde. All of such solvents are aliphatic oxygenated solvents.

The invention may be illustrated by, but not restricted to, the following procedures exemplifying the application of the method to each of the three classes referred to in the preceding paragraph:

A. Lower Molecular Weight Aliphatic Aldehydes with Ethyl Cyanoacetate.

A mixture of 56.6 grams (0.5 mole) of ethyl cyanoacetate, and 0.6 mole of the freshly distilled selected lower molecular weight aliphatic aldehyde, and 1.0 gram of palladinized charcoal and 80 cc. of glacial acetic acid was placed in a 500 cc. "Pyrex" (Registered Trade Mark) bottle (with an arrangement for permitting hydrogenation), and to this mixture was added a solution of 2 cc. (0.02 mole) of piperidine in 20 cc. of glacial acetic acid and hydrogenation at a pressure of 1 to 2 atmospheres was begun immediately. Reduction was rapid and exothermic. In 1 to 3 hours the theoretical amount of of hydrogen (0.5) mole was taken up and absorption ceased. The resulting individual ethyl alkylcyanoacetates were isolated by filtering the reaction mixture, adding 50 cc. of benzene to the filtrate and washing the resulting solution with two 50 cc. portions of 10% sodium chloride solution followed by three 25 cc.

portions of water. Wherever an emulsion formed at this point, it was broken by the addition of a few cc. of ether. The combined washings were extracted with two small portions of benzene which were then combined with the original benzene solution, and the combined benzene solutions were distilled through a Widmer column under reduced pressure. No ethyl cyanoacetate was recovered in the forerun, and the individual ethyl alkylcyanoacetate was recovered and only a small distillation residue remained, the ethyl alkylcyanoacetate being readily purified by distillation.

When aldol was employed as the starting aldehyde, 0.7 mole of hydrogen were absorbed and 55.5 grams (66%) of ethyl *n*-butylcyanoacetate was obtained.

B. Branched Chain, Higher Molecular Weight Aliphatic Aldehydes and Benzaldehyde.

A mixture of 56.6 grams (0.5 mole) of ethyl cyanoacetate, and 0.6 mole of the selected aldehyde, and 6.0 grams (0.05 mole) glacial acetic acid and 150 cc. of dioxane (purified by boiling over sodium for 48 hours and redistilling) was placed in a 500 cc. " Pyrex " (Registered Trade Mark) bottle, as in example A, and cooled in an ice salt mixture to 4° C. 2.0 cc. (0.02 mole) piperidine was added dropwise to the mixture during approximately 10 minutes with occasional swirling. The temperature rose to 20° C. and the solution became turbid. When the addition was complete, 1.0 gram of palladinized charcoal was added and the mixture was hydrogenated as in the preceding example. With the indicated aliphatic aldehydes, heat was evolved and reduction was complete in about 4 hours. With benzaldehyde, hydrogen absorption was fairly slow even when the reaction was carried out at 60° C. The esters were isolated and purified as in the preceding example. In the case of the indicated aliphatic aldehydes, no ethyl cyanoacetate was recovered, and only small distillation residues were left. With benzaldehyde there was a forerun of ethylcyanoacetate (8.0 grams) and appreciable residue (35 grams).

C. Aliphatic Ketones.

56.6 grams of ethylcyanoacetate (0.5 mole), and 0.55 mole of the selected ketone, and 3.9 grams of ammonium acetate (0.05 mole), and 6.0 grams (0.1 mole) of glacial acetic acid, and 100 cc. of 95% ethanol and 1.0 grams of palladinized charcoal were placed in a 500 cc. " Pyrex " (Registered Trade Mark) bottle and hydrogenated as in the preceding examples. The reactions with the ketones were also exothermic but to a lesser degree than with the aldehydes of the preceding examples. The esters were isolated and purified as in example A.

The ethyl monoalkylcyanoacetates obtained according to the preceding examples are represented by the formula $XCH(CN)COOC_2H_5$, in which X represents the alkyl group attached as a result of the method of the invention to the methylene carbon of the starting ethyl cyanoacetate, and are identified by the alkyl group in the following table, which also includes the ketone or aldehyde used as starting material:

| Alkyl group, X | Ketone or Aldehyde used in preparation | Reaction time (hrs.) | Boiling Pt. °C. | Mn |
|---|---|---|---|---|
| | According to procedure of Example A | | | |
| Ethyl | Acetaldehyde | 2.5 | 84—85 | 7 |
| *n*-Propyl | Propionaldehyde | 3 | 95—96 | 8 |
| *n*-Butyl | Butyraldehyde | 1.3 | 108—109 | 8 |
| | According to procedure of Example B | | | |
| Isobutyl | Isobutyraldehyde | 4 | 98—99 | 7 |
| Isoamyl | Isovaleraldehyde | 4 | 113—114 | 7 |
| *n*-Heptyl | Heptaldehyde | 4 | 111—113 | 1 |
| Benzyl | Benzaldehyde | 16 | 118—122 | 0.4 |

| Alkyl group X. | Ketone or Aldehyde used in preparation | Reaction time (hrs.) | Boiling Pt. °C. | Mn |
|---|---|---|---|---|
| | According to procedure of Example C | | | |
| Isopropyl | Acetone | 5—6 | 89—91 | 8 |
| sec. Butyl | Methylethyl ketone | 4.5—6 | 99—100 | 7 |
| 1-Methylbutyl | Methylpropyl ketone | 11 | 111—112 | 8 |
| Cyclohexyl | Cyclohexanone | 4—6 | 138—139 | 8 |
| 1,3-Dimethylbutyl | Methylisobutyl ketone | 8—11 | 117—119 | 8 |
| 1-Methylhexyl | Methylamyl ketone | 9 | 135—137 | 8 |
| 4-Heptyl | Dipropyl ketone | 7—22 | 131—132 | 7 |
| 1-Methylheptyl | Methylhexyl ketone | 5—6 | 112—115 | 1.0 |

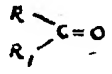
In the preceding table, the products resulting from using heptaldehyde, methylisobutyl ketone, methylamyl ketone, and methylhexyl ketone as the carbonyl compound starting material are new compounds suitable for use as intermediates for other chemically useful substances.

While the invention has been illustrated by the above specific procedures involving the use of piperidine and ammonium acetate as the condensing catalyst, other nitrogen bases or ammonium salts of fatty acids, particularly the salts of nitrogen bases, with or without acetic or other fatty acids, may be used with advantage. In general, the effectiveness of a salt as a condensing agent or catalyst in the process of the invention depends to a reasonable measure upon its solubility in the reaction mixture. Condensation catalysts which are typical of those used in accordance with the invention and which may be used with advantage are the following:

ethylene diamine diacetate
diethanolamine acetate
aniline acetate
piperidine butyrate
piperidine oleate
diethylamine acetate
glycine salt
sodium acetate
potassium acetate.

Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. A process for the preparation of a monoalkyl or -aralkyl cyanoacetate alkyl ester which comprises reacting a ketone or an aldehyde of the general formula—



wherein R is hydrogen, an alkyl (including cycloalkyl) or an aryl radical and $R_1$ is an alkyl (including cycloalkyl) radical or may be an aryl radical when R is hydrogen, or R and $R_1$ may together form a cycloalkyl radical with a cyanoacetic alkyl ester in the presence of an alkali metal salt of a fatty acid, or an acid amide, or a soluble salt of a nitrogen base, in the presence of hydrogen and a hydrogenation catalyst.

2. A process as claimed in claim 1 wherein the nitrogen base is an ammonium or amine salt.

3. A process as claimed in claim 2 wherein the ammonium or amine salt is an acetate.

4. A process as claimed in any one of the preceding claims wherein the nitrogen base is employed in the presence of a fatty acid.

5. A process as claimed in claim 4 wherein the fatty acid is acetic acid.

6. A process as claimed in any one of the preceding claims wherein the reaction is carried out in the presence of an inert solvent.

7. A process as claimed in claim 6 wherein the inert solvent is benzene or alcohol or dioxane or glacial acetic acid.

8. A process as claimed in any one of the preceding claims wherein the hydrogenation catalyst is a metal of the platinum or palladium triads of elements.

9. A process as claimed in claim 8 wherein the hydrogenation catalyst is platinum.

10. A process as claimed in claim 9 wherein the hydrogenation catalyst is palladium.

11. A process as claimed in claim 10 wherein the catalyst consists of palladium supported on charcoal.

12. A process as claimed in claim 1 wherein the ketone is methyl *n*-propyl ketone.

13. A process as claimed in claim 12 wherein the alkyl cyanoacetate is a lower alkyl cyanoacetate.

14. A process as claimed in claim 13 wherein the alkyl cyanoacetate is ethyl cyanoacetate.

15. A process for the preparation of a monoalkyl or -aralkyl cyanoacetic ester substantially as described in any one of the specific examples hereinbefore set forth.

16. A mono-alkyl or -aralkyl cyanoacetic ester whenever prepared or produced by the process claimed in any one of the preceding claims.

Dated this 16th day of May, 1945.
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